Fear and wonder

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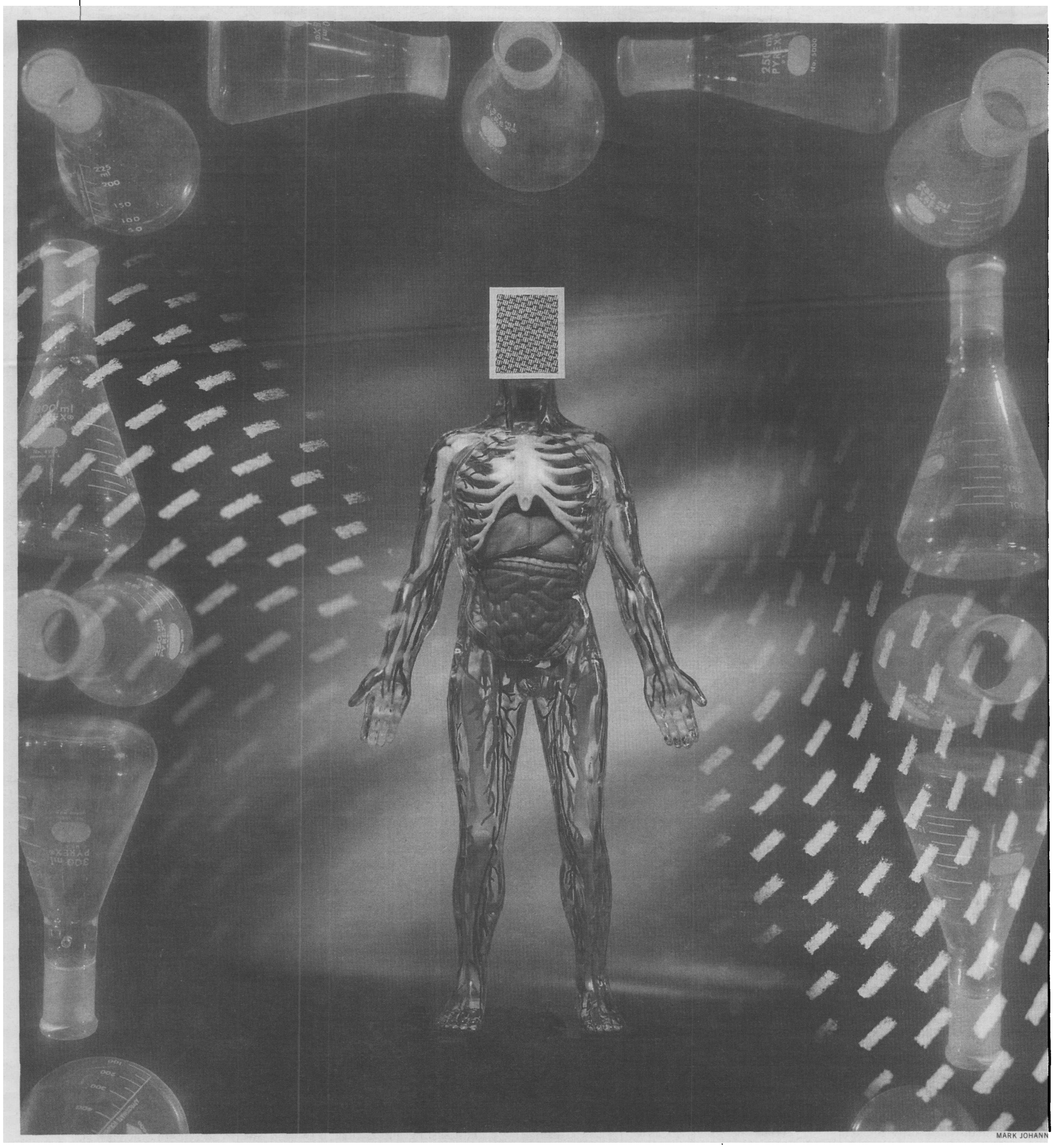
The Village Voice; Sep 30, 1997; 42, 39; ProQuest
pg. 36

PART ONE OF A SERIES



MARK JOHANN

HOW GENETICS IS CHANGING OUR LIVES By Mark Schoofs

FEAR AND WONDER

Absentminded Pieter de Jong is trying to remember where the human DNA is kept. He opens a refrigerator, pulls out a little plastic tray, and, brushing off the frost, reads an identification tag. "Sorry," he says, "this one's rat DNA."

He opens an identical refrigerator and pulls out an identical tray, which looks like a miniature cupcake tin. Inside every tiny cup are millions of bacteria, each of which has, to use de Jong's phrase, "slurped up" a snippet of foreign DNA. But what kind of DNA? "Dog," he says, smiling sheepishly.

As he keeps opening refrigerator doors, de Jong explains that his center is creating a DNA "library" for mice, rats, dogs, corn, rice, malaria, slime mold—and human beings, too. A library is a complete reference set of an organism's actual DNA, broken up into short segments scientists can work with. The library de Jong directs, at Buffalo's Roswell Park Cancer Institute, is the world's largest supplier of DNA fragments. Right now, he is

CONTINUED ON PAGE 38

SCHOOFS

CONTINUED FROM PAGE 37

compiling a new set of human DNA for the international Human Genome Project, which is sequencing our entire genetic code.

But where *is* the human DNA? De Jong opens another refrigerator and, voilà: these plastic trays contain fragments of the stuff that, under the right conditions, wouldn't generate a rat or a patch of mold but a person. A complete human library consists of 1200 such trays, and in this refrigerator there are shelves and shelves of them waiting to be shipped to laboratories all over the world, where researchers will put the DNA through every conceivable manipulation. They will cut it up, paste it into different animals, mutate it, then splice it into animals again, and subject it to chemical and electrical reactions. In short, they will fiddle with it until they figure out how the simple yet intricate double helix works its wonders.

They are far from that knowledge now. The discovery of new genes may appear routine, and cloning may seem like the ultimate breakthrough, but in fact barely 2 per cent of the vast human genome has been sequenced. Down the road lie discoveries and uses that can barely be imagined. Yet DNA is already being used to capture criminals, develop drugs, confirm paternity, fathom the mysteries of evolution, make crops hardier, fuel the rapidly expanding $11 billion biotech industry, and test embryos to decide which shall live and which shall not.

When the Human Genome Project finishes by 2005, our entire genetic blueprint will fit onto a single CD-ROM. After that, says MIT geneticist Eric Lander, "it will be hard to explain to students how we did biology without the human genome."

Still, some people note that, despite budgeting $3 billion to map and sequence the genome, not a single genetic disease has been cured. So is the project overhyped? "I think it's probably underhyped," responds Francis Collins, director of the federal government's National Human Genome Research Institute. "If you ask the average person what the Human Genome Project is and what it will do, most people will say, Huh? But when the history of science is written 100 years from now, this will be seen as the greatest scientific project of the century, maybe of all time."

'UNTIL THE LAST FEW YEARS, WE HAD NEVER BEEN ABLE TO LOOK INTO THE MOLECULAR CODING OF OUR INHERITANCE. THAT IS A STAGGERING CHANGE. IT'S LIKE ASTRONOMY AFTER THE TELESCOPE, OR MICROBIOLOGY AFTER THE MICROSCOPE.'

Geneticist David Galas agrees. He used to head the precursor of the Human Genome Project, which operated under the auspices of the Department of Energy. Now he is president of the biotech firm Darwin Molecular. "Until the last few years, we had never been able to look into the molecular coding of our inheritance. That is a staggering change," he says. "It's like astronomy after the telescope, or microbiology after the microscope."

FOR SOCIETY, IT will be more like life after atomic energy. Genetics can do tremendous good or wreak unspeakable horrors. The double helix is a double-edged sword, and how it will cut depends on how society deploys it.

Most Western countries have banned human cloning, and Congress is now debating a bill that would forbid employers and health insurers from discriminating based on genetic information. Called the Slaughter bill, after its prime sponsor Louise Slaughter (D-NY), the law would also offer privacy protections. But the Clinton administration has proposed a loophole big enough to drive a truck through. Any law enforcement or intelligence officer—which could include agents of the CIA and the departments of state, treasury, and defense—could gain access to any citizen's complete medical records, DNA included, without a *warrant*, and without the person's knowledge or consent.

Even if this loophole is closed, the Slaughter bill *only* addresses the easy issues. Ahead lie a series of ethical, legal, and cultural crises. They will challenge each of us, and ultimately be resolved by public opinion and private conscience.

▶ Tests for drug abuse are now commonplace, but they were first introduced in professions where public safety is at stake. Should genetic tests be used in a similar way? Should someone with a predisposition to, say, Alzheimer's be allowed to become president? Fly an airplane? Drive a school bus? Take custody of a child after a divorce? Genetic fitness has already arisen in a custody hearing.

▶ Is it child abuse if parents knowingly have a baby with an inherited disorder? Some legal and ethical writers argue that it is. Gillian Woollett, who monitors genetics for the Pharmaceutical Research and Manufacturers of America, doesn't have an answer to this dilemma, but she has a question that cuts right to the heart of it: "At what point do you become accountable for passing on your genes?"

▶ Should law enforcement be allowed to collect DNA fingerprints of people whom they arrest? If so, for what crimes? Rape and murder? All felonies? Misdemeanors? Should one be required to give DNA samples to get a security clearance? A passport? A driver's license?

▶ Genetic testing will predict who is at risk for certain diseases, and who is not. In his book *The Language of Genes*, geneticist Steve Jones speculates that "some individuals may be able to drink, smoke, or eat lard with impunity. Perhaps it will become possible to choose the vices best fitted to ourselves." That's the upside—but would you want to know you are likely to get a deadly disorder, such as Lou Gehrig's Disease, for which there is no cure?

▶ Just what is disease? Sydney Brenner, one of the world's most respected geneticists, says there's a range. At one extreme are conditions that cause "agony or premature death. At the other end," he says, wryly, "is cosmetic correctness, like hair growing out of the ears. In between are things one may wish to debate." Deaf people consider themselves a minority, like gays or blacks, and have protested genetic "cures" for deafness. Is it a cure to give a child the ability to hear, or is it an act of genocide? Is homosexuality a disease? Albinism? What about height? In her book *Exploding the Gene Myth,* Harvard biologist Ruth Hubbard noted that human growth hormone was recommended for the shortest 3 per cent of the population—but, of course, there will *always* be a shortest 3 per cent, even if the average height increases dramatically.

▶ Will eugenics make a comeback? Already, scientists are searching for genes that correlate with IQ. The abuse of genetics and IQ testing forms one of the darkest chapters of American history. In the first half of this century, the United States sterilized about 25,000 people—with the Supreme Court's blessing. Justice Oliver Wendell Holmes approved the sterilization of a "feeble-minded" woman and her young child because "three generations of imbeciles are enough." Nazi Germany copied

American eugenics laws and extrapolated them all the way to concentration camps, but such ideas did not perish with the Third Reich. In 1994 authors Charles Murray and Richard Herrnstein published *The Bell Curve*, which argued that on average blacks are less intelligent than whites and that programs such as Head Start are a waste of money because cognitive ability is inherited. Under the skin, DNA shows that the races are far more similar than different. But even if genetics weakens racism, will it lead to a new bigotry, one based not on skin color but on DNA?

These issues merely touch the surface of what will arise as genetic manipulation expands what science is able to do to people. There is more to destiny than DNA, but change the genes and you can change a person. Political revolutions alter the fate of nations, but the genetic revolution can alter the future of the human species.

It will certainly change the way we think about ourselves and our place in nature. To study genes is to study life itself.

THE FUNDAMENTAL CONCEPT of genetics hasn't changed much in the 130 years since Austrian monk Gregor Mendel cross-bred his pea plants and figured out that living beings carry hereditary "elements." Twentieth-century science determined that Mendel's elements are molecules that interact according to the laws of chemistry, and in 1944, deoxyribonucleic acid, or DNA, was proven to be the hereditary molecule.

DNA is made of four chemicals: adenine (A), cytosine (C), guanine (G), and thymine (T). The new film *GATTACA* is a reference to these "letters" of our instruction manual; their sequence tells the body what to do. A change of just one letter can sometimes spell the difference between health and disease.

It is commonly thought that DNA creates life on its own. In fact, DNA interacts with its molecular environment through an unimaginably complex web of chemical reactions. It responds to chemicals in the womb, in the body, in the food we eat and the air we breathe. Every living substance in the body, from bone to blood, along with every action of the body, from mobilizing antibodies in the immune system to firing synapses in the brain, is created by an interaction with DNA.

Genetics has reduced "the mystery of life to chemistry and atoms," says researcher William Haseltine, who now heads the biotech company Human Genome Sciences, Inc. He sees this as a validation of Buddhist philosophy—"What we describe as living is an extension of what we would describe as dead." But others draw very different conclusions from genetic knowledge. "We are machines for propagating DNA," writes Oxford zoologist and spirited atheist Richard Dawkins in his book *The Selfish Gene*. "It is every living object's sole reason for living."

Whatever one's perspective, genes are simply sequences of the four letters that do something—usually make proteins, the building blocks of all living organisms. Coiled in the nucleus of every cell is the entire genome—3 billion letters that would stretch six feet if laid out end to end. But most of it does not do anything. Scientists call it "junk DNA."

Mountains of detail have been accumulated since the discovery that Mendel's elements were made of DNA, but it is mostly commentary. The huge advance in genetics since Mendel is not *intellectual*, it is *technological*. Now, scientists can manipulate genes, shift them around, change them. DNA is not an idea, it is a tool. Geneticists, says NYU professor Dorothy Nelkin, "are really engineers."

But that is not how genetics is widely perceived. Complex problems get reduced to a simplistic explanation. In the popular mind, there is a "gene for" everything from intelligence to criminality, from cancer to alcoholism. "The stuff that crosses my desk is mind-boggling," says Nelkin, author of *The DNA Mystique*. "I just came across a newspaper clip that says women are genetically predisposed to be in the funeral industry."

In fact, very little is *explained* by genes. Even knowing the full sequence of the human genome won't "answer the hard questions," says Lander. "It just gives you the tools to begin to answer them." We still don't understand even the simplest kind of hereditary disease, such as Huntington's chorea, which is caused by a mutation in just one gene. This summer researchers made the first major breakthrough in understanding how that mutation might lead to the slow destruction of the brain—but this came four years after the discovery of the mutation. "The hype has come from exaggerating what genetics will be able to do immediately, and from presenting it as some sort of panacea for other research," says Galas. "It's fundamental, but it doesn't automatically solve the problem."

Not even for Huntington's, where the mutated gene is the first domino in a series that leads inexorably to death. Other diseases are much more complicated. By the latest estimate, more than 55 per cent of women with a mutation on a gene called BRCA-1 will develop breast cancer—but why not 100 per cent? No one knows. A year ago, researchers announced they had found a gene that influences anxiety. Unlike other genetic explanations for behavioral traits—such as alcoholism—which have proven false, this finding may well hold up, because the gene apparently influences how the brain processes serotonin, the neurotransmitter targeted by Prozac. But even the gene's discoverers say it is only one of many factors that influence anxiety. As Yale brain researcher Martha Constantine-Paton says, "The things that make one person anxious may just make another person conscientious." So when it comes to the most profound questions of human character, what can DNA tell us?

FOR AN ANSWER, head to the Upper East Side and have dinner at Twins Restaurant, owned and staffed by identical twins. Natural clones, "monozygotic" twins are split from a single fertilized egg, and so almost certainly share all their DNA. Studying twins is the classic way to tease apart nature and nurture, and it continues to be one of the most powerful.

Waiters Sabine and Shane Rice look remarkably alike. On a trip to France, Shane wanted to go home early, and Sabine had a ticket that fit her schedule. Rather than hassle with the airline, the sisters simply switched tickets and passports. No one noticed.

Traveling has highlighted their similarities in deeper, almost uncanny ways. While one was in Europe and the other in the States, they each decided, without knowing the other was doing the same, to get their first tattoo. A year later, separated again by the Atlantic Ocean and unbeknownst to each other, they each started smoking.

Sabine and Shane grew up together, but even twins reared in separate homes have such stories. One of the most famous, having made the pages of *The New Yorker*, involves Jack Yufe, who was reared as a Jew, and Oskar Stöhr, who was reared by Germans and joined the Hitler Youth. When the brothers were reunited as adults, they discovered uncanny similarities: Both flushed the toilet before using it, both were natural mechanics, and both sneezed in elevators to startle fellow riders.

This pair participated in the large and ongoing Minnesota Study of Twins Reared Apart. It found that, for IQ and psychological traits such as neuroticism and extroversion, identical twins score much more closely than fraternal twins. And identical twins raised apart don't score much differently from identical twins raised together.

From this and similar studies, researchers estimate that genes account for between

CONTINUED ON PAGE 40

SCHOOFS

CONTINUED FROM PAGE 39

40 and 60 per cent of the variation in human psychological traits, and between 40 and 70 per cent of the differences in IQ. But these percentages only describe the variations within a group; they cannot be applied to an individual. A long chain of causal events leads from DNA to any given trait. "It is a bit like asking what percentage contribution George Washington made to the establishment of the United States," writes Ari Berkowitz, a neurobiologist at the California Institute of Technology. "Any sensible answer would not be a percentage; it would be a story."

But the similarities of twins reared apart hint at the plot of this nature/nurture tale. "A kid whose genetic makeup leads him to climb around and fall down and break things will be treated differently by his parents than a more sedentary or fearful sibling," explains Minnesota researcher David Lykken. "By the time they get to school, people will react to them differently, and the kids themselves will seek out environments congenial to their temperament. Their different experiences are the immediate causes of their personality configurations, but those experiences are to a large extent produced by their genetic steersmen."

The popular imagination has been grabbed by cloning, which raises the possibility of people with the same genetic steersmen being reared in different wombs and even living in different historical epochs: How similar would they be? But anyone who thinks about twins quickly realizes that the most profound mystery lies with those who are conceived and raised together: Having the same nature and nurture, why do they have any differences?

The answer helps explain the role of DNA. It also illuminates the essence of biology.

WHEN SHANE FAILED her first driving test, Sabine passed it for her the very next day. Chuckling at the memory, Sabine says, "The lady was like, 'Gee, you're driving so much better than yesterday!' " Unlike the passport caper, which was essentially frivolous, there was a serious reason Sabine took her sister's test: Shane is afraid of driving (and of flying, too); Sabine isn't.

There are other differences. Sabine is more career oriented, taking classes to get a job in computer graphics. Shane, on the other hand, is happy waiting tables, because she likes the people at Twins and doesn't want to deal with office politics and backstabbing. Shane left home at 17, and even endured two weeks living on the streets, because she no longer wanted to take money from her wealthy father. Sabine went to college, courtesy of her parents. Shane talks in rambling, unpunctuated paragraphs, Sabine in pointed quips.

Twin studies have documented all kinds of differences. Twins have different fingerprints, and they differ in height and weight. "Identical twins do not look as alike as people think they do," says Lykken's colleague Thomas Bouchard. "It's easy to say, 'This one looks more attractive.' " Indeed, Lykken has found that the spouses of twins are not usually attracted to the other twin.

There are deeper differences. If one twin is gay, the other is usually straight. If one twin gets diabetes, there's only a 30 per cent chance the other will get it, too. Same with schizophrenia. The odds that twins will both get these two diseases are much higher than for regular siblings, but they aren't anywhere near 100 per cent. Brain waves, as well as the size and shape of the corpus callosum, are far more similar for identical twins than for unrelated people, but they are not identical.

This shows how intricate and fragile is the journey from DNA to a person. Many things can send the "genetic steersman" off course. A tremendous body of literature records the damage to children caused by poor nutrition, inadequate mental stimulation, and plain old lack of love. Long before a baby has a chance to crawl around, all the brain's billions of neurons are made and put in place. Before a mother gives birth, her health has tremendous influence on how this delicate genetic process unfolds.

Even after a child is grown, DNA keeps interacting with the environment, and new generations of cells bear the imprint of that interaction. Many cancers are caused by genetic changes produced by environmental "insults." Still, many people think that destiny is set in a fertilized egg.

The influence of DNA can easily be exaggerated for political purposes. University of Pittsburgh professor Herbert Needleman documented the devastating effect of lead on the development of IQ and behavior. The industry argued that lead didn't cause low intelligence, he recalls, but rather "kids who are dumb put more dirty things in their mouths." By this reasoning, low IQ was the cause of excess lead in the body, rather than lead being the cause of low IQ—an idea that has been thoroughly debunked. "We looked at Head Start and said that program didn't work very well," notes Leo Chalupa, a neuroscientist at the University of California at Davis. "But what the hell were they doing taking kids at five years old? They should have been starting at conception."

By the time twins reach adulthood, the biggest difference between them lies in their choice of romantic partners. Researchers have found that twins often share political and religious views, as well as hobbies and interests. But there is no correlation in their choice of spouse. Sabine, for example, likes independent men, while Shane likes needy ones. "She likes being the rescuer," explains Sabine, "so she's always getting these guys who are puppies. I call her the walking humane society." Lykken, who carried out the research on romance, puts a scientific spin on what poets have always known: Love is "one of the few human actions that can't be attributed either to environmental background or genetic tendencies, but is a matter of chance."

"People confuse similarity with identity," says professor Nancy L. Segal, a twin researcher from Cal State Fullerton, who is herself a fraternal twin. "Our psychological tools can get at basic similarities, but they can't get at fine distinctions." So, is reading a psychological profile like looking at the back of a tapestry? "That's a great analogy," says Bouchard. He points out that pyschological scores sum up the answers to many different questions, so people could arrive at the same outcome even though they answered each question differently.

DNA designs us to be flexible. This is perhaps the most profound thing we have learned about genetics. It's a paradox, but our genes predetermine that we are not predetermined.

The immune system, for example, does not come into the world with a full stockpile of antibodies. Instead, it makes them as it encounters individual viruses and bacteria, making the immune system a historical record of an individual's skirmishes against disease.

The brain is also shaped by the vagaries of life. "The brain is not a computer, and people who say it is are stupid," snaps Chalupa. "The physical, synaptic connections are being changed slightly throughout life. They are different now than they were two minutes ago, although the change is very minute."

The brain cannot be hardwired for the simple reason that it *must learn*. Experiences and memories shape and reshape its circuitry, strengthening those synaptic connections that fire often and letting others weaken. The brain is most flexible before sexual maturity—if you learn a language after age 11 you will always speak it with an accent—but it never hardens completely, because it has been designed to constantly adapt to new situations. When an infant comes into the world, its genes have created a huge abundance of neurons and synapses; as the

CONTINUED ON PAGE 43

SCHOOFS

CONTINUED FROM PAGE 40

baby matures, that number dwindles, as the synapses that don't get used are simply eliminated. Yale neuroscientist Pasko Rakic compares this process to sculpture: "You are constrained by the size and shape of the stone, but within that size and shape, you can make an infinite number of figures."

Psychological traits are neutral. Sculpted in one way, a trait can be a boon; chiseled another way, it can be harmful. That's why Lykken is agitating for legislation that would forbid people from raising their children without a license from the state. "Why should people who we would not dream of trusting with an adopted child be allowed to produce biological children?" he asks. "That's unfair to the children."

Critics smell bigotry: Lykken uses lightning-rod terms such as "single moms" and "crack addicts," and he himself has acknowledged that minorities would bear the brunt of his legislation. But Lykken, who has said he is making his near-totalitarian proposal to draw attention to the problem of bad parenting, is not advocating a *genetic* test for parents. He's not worried that people will transmit "bad genes." He notes that some people are born almost fearless—and that trait appears to be genetically influenced. Such a child, says Lykken, "won't react well to punishment, because punishment works by fear of future punishment." Frustrated parents often intensify their reprimands, but the sad and unintended "result is often that the kid is driven out into the street, and he becomes delinquent." This may be why some studies have linked fearlessness to crime.

But that same kid might have a different destiny if his parents relied "less on punishment and more on cultivating in the child a sense of pride. That kid may turn out to be a hero. The psychopath and hero are twins on the same genetic branch, and the difference is experience."

Lykken reflects on the identical twins who ended up as different as two people can be—a Jew and a Nazi. If they had been switched, with the one who was raised a Jew being given to the German mother and vice versa, he speculates that the one who lives as a Jew now would have become a Nazi. With twins, he says, life stories are "fungible."

Here, then, is the ultimate difference between biology and physics. While physics and chemistry are timeless and absolute, biology is inextricably intertwined with chance and contingency. "Biology was initially viewed as a very soft science, because very little could be put into precise laws," says Galas. "Now that has changed very dramatically. Biology has become a hard science in some sense." DNA is a string of chemicals, and unraveling its chemical reactions makes biology far more precise and predictable. Still, says Galas, "biology cannot ever be anything like chemistry because it always bears the imprint of history—things could have been quite different."

Or, as Bouchard says, "without an environment to grow up in, DNA is just a moist spot on the floor." V

Part Two: Genetics and evolution

Research assistance: Ebony-Anne Smith, Dennis Lim